Calciphylaxis: An In-Depth Analysis of Etiology, Risk Factors, and Treatment Modalities

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Abstract

Calciphylaxis is a rare and life-threatening disease characterized by calcium deposition in the small arteries of the skin and subcutaneous fatty tissue, leading MM to necrotic, severely painful lesions that are often prone to infection and contribute to a high mortality rate. The disease is primarily associated with advanced chronic kidney disease, particularly in patients with end-stage kidney disease (ESKD). Despite its severe outcomes, calciphylaxis remains incompletely understood. The underlying mechanisms involve a complex interplay of metabolic and vascular factors, making effective treatment and management challenging. This study examines the disorder's current understanding, its pathophysiology, associated risk factors, diagnostic challenges, and emerging treatment strategies. The information from this review can shed light on the disease's underlying mechanisms and highlight the importance of early diagnosis and multidisciplinary management in improving patient outcomes.

Introduction

Calciphylaxis, also known as calcific uremic arteriolopathy, is a rare and serious disorder affecting the skin and subcutaneous tissue. It is characterized by painful skin lesions accompanied by necrotic skin and subcutaneous fatty tissue. These lesions involve mostly the thighs, buttocks, and body parts of more fat tissues, and primarily appear among patients with advanced chronic kidney disease. Calciphylaxis is a life-threatening vascular disease resulting from calcium deposition in the small arteries of the skin and subcutaneous adipose tissue (1).

It is a lethal disease with high mortality and morbidity and has an estimated 6-month survival of approximately 50% (2). Bryant and White first described the disease in 1898 (3). Later, the term “calciphylaxis” was coined by Hans Seyle in 1962 (4-5).

Epidemiology, Risk Factors, and Pathophysiology

Calcyphylaxis is most commonly associated with chronic kidney disease, especially in patients undergoing maintenance dialysis. The largest nationwide study to date estimates an incidence rate of 3.49 per 1,000 patient-years among patients receiving maintenance hemodialysis (6).

In kidney failure patients, the enzyme 1-α hydroxylase, which converts vitamin D (25-hydroxyvitamin) to 1,25-hydroxy vitamin D, the biologically active form, is less expressed in the kidney. This decreased synthesis of active vitamin D causes poor calcium absorption from the gut. The resulting reduced kidney function lacks proper phosphate and calcium excretion, causing activated parathyroid gland function, known as secondary hyperparathyroidism; this condition can cause increased serum phosphate and calcium levels, facilitating arterial calcification and calciphylaxis.

In addition to renal failure, other notable risk factors for calciphylaxis include obesity, diabetes mellitus, female sex, hyperparathyroidism, use of warfarin, vitamin K deficiency, and some other medical conditions (1).

Calciphylaxis is a vaguely understood disorder, and its pathogenesis involves complex interactions between metabolic and vascular factors. The skin lesions of calciphylaxis are attributed to reduced arterial blood flow (7-8), caused by calcification, and thrombus formation primarily involving the dermo-hypodermic (skin-cutaneous) arterioles.

Microvascular (small blood vessel) calcification occurs (9) likely through an active process involving the upregulation of factors in osteogenesis (bone formation) and bone remodeling, including bone morphogenetic protein-2 (BMP-2), runt-related transcription factor 2 (RUNX-2) (1,10-11) and osteopontin (12-13). Adipocytes (fat cells) may also play a significant role in vascular calcification (14). Ongoing vascular endothelial (inner layer) injury causes cutaneous arteriolar narrowing and thrombosis, leading to tissue infarction (15).

Hyperparathyroidism and Vitamin D

Hyperparathyroidism, active vitamin D administration, hyperphosphatemia, and elevated plasma calcium $\times$ phosphorus product (Ca$\times$P) are also implicated in the pathogenesis of calciphylaxis.

Animal models suggest a role for hyperparathyroidism, showing that the administration of large amounts of parathyroid hormone can induce ischemic (lack of blood supply) skin necrosis (death of skin cells) (16).

Moreover, parathyroidectomy (parathyroid gland removal) has been associated with clinical improvement in some patients (2,17). The benefit of parathyroidectomy may be attributed to the uptake of calcium and phosphate into the bone, which occurs following surgery and as a result,

lowers the serum calcium and phosphorus levels.

However, there have been no clear studies of the effectiveness of parathyroidectomy in treating calciphylaxis. Most patients with severe hyperparathyroidism do not develop skin necrosis, and many patients with calciphylaxis do not have hyperparathyroidism, indicating that other causes are responsible for calciphylaxis(18-19). Studies that report comprehensive data on PTH (parathyroid hormone) levels months to years before calciphylaxis diagnosis are needed to determine the pathogenic role of hyperparathyroidism in calciphylaxis.

In experimental models, high-dose vitamin D administration has been shown to induce calciphylaxis (20-21). This observation may be relevant, as calcitriol (an active vitamin D) and other vitamin D analogs are routinely administered to treat secondary hyperparathyroidism seen in ESKD patients. Active vitamin D and its analogs may contribute to calciphylaxis indirectly through increasing serum calcium and phosphate, or directly through their effect on the vasculature.

Genetic factors may also play a role in the development of calciphylaxis, with genes encoding vitamin D receptor (rs17882106 and rs10783223) and Fibroblast growth factor 23 (rs7310492, rs11063118, and rs13312747) being potentially implicated (22).

Inhibitors of Vascular Calcification

Deficiencies in inhibitors of vascular calcifications may contribute to the pathogenesis of calciphylaxis. Two important inhibitors include Fetuin-A (2-Heremens-Schmid glycoprotein) and matrix Gla protein (MGP).

Fetuin-A

Fetuin-A is an abundant serum glycoprotein that binds calcium and phosphate in the circulation, thereby forming calciprotein particles that aid in clearing the circulation of excess Ca✕P (23). In animal models, Fetuin-A limits organ and soft-tissue calcification and vascular calcium deposition (24). Low Fetuin-A levels correlate with chronic inflammation and cardiovascular calcification in patients on hemodialysis (25). Compared with serum Fetuin-A levels in healthy individuals, Fetuin-A levels in patients on hemodialysis are lower and have a diminished capacity to inhibit ex-vivo (experimental) Ca✕P precipitation (26).

Matrix Gla Protein (MGP)

MGP is a mineral-bonding extracellular (outside of cell) matrix protein that is synthesized by vascular (blood vessel) smooth muscles, endothelial, and chondrocytes (27). In animal models, MGP has been shown to inhibit calcification of arteries and cartilage (28). Warfarin, a vitamin K antagonist, is a risk factor for calciphylaxis and is known to impede vitamin K-dependent

mechanisms, including the carboxylation of MGP; this inhibition may be a mechanism by which warfarin increases the risk of calciphylaxis (19,27,29).

The calcification inhibitor pyrophosphate is degraded by tissue-neutral alkaline phosphatase, which is in turn inhibited by adenosine (30).

Other Inhibitors

Other inhibitors of calciphylaxis include Klotho, pyrophosphate osteoprotegerin, and magnesium.

α-Klotho

α-Klotho is a membrane protein that is highly expressed in the kidney. Levels of Klotho decrease with progressive chronic kidney disease (CKD) (31). Klotho increases phosphate excretion and inhibits phosphate uptake by vascular smooth muscle (32).

Pyrophosphate

Pyrophosphate is produced by vascular smooth muscle cells and inhibits the formation of hydroxyapatite crystals, which are a key component of calciphylaxis. Pyrophosphate is reduced in patients with CKD, particularly those on dialysis (33). In laboratory studies, the administration of pyrophosphate has been shown to reduce ectopic calcification without apparent adverse effects on bone (34).

Osteoprotegerin

Osteoprotegerin competes with the receptor activator of NF-KB ligand (RANKL) and its receptor, RANK, on osteoclast (bone resorption cell) precursor cell membranes (35). While RANKL promotes vascular calcification, osteoprotegerin protects against it (36). However, the clinical effects of osteoprotegerin activity are not completely clear, as both low and high serum concentrations of osteoprotegerin have been associated with vascular calcification (37-38).

Magnesium

Many experimental studies have suggested that the administration of magnesium prevents vascular calcification (39-41). Potential mechanisms include the inhibition of calcium-phosphate crystal growth in the circulation, thereby decreasing calcium-phosphate deposition and preventing the phenotype (observable character) changes of vascular smooth muscles to osteoblasts (bone formation cells) (39).

Chronic Inflammation

Chronic inflammation is another significant factor in calciphylaxis. Conditions such as connective tissue disease, Crohn's disease, and autoimmune conditions have been reported in patients with uremic and nonuremic calciphylaxis (25,42-43).

Epidemiology

While calciphylaxis is commonly associated with ESKD, it can also occur among patients with normal kidney function (42-45). In such cases, the most commonly associated underlying conditions include primary hyperparathyroidism (28%) malignancy (22%), alcoholic liver disease (17%), and connective tissue disorders (4%). Furthermore, prior treatment with glucocorticoid and warfarin has been linked to the development of calciphylaxis in non-ESKD patients.

Diagnosis of Calciphylaxis

Clinical Manifestation

Early skin lesions are painful subcutaneous indurated nodules or plaques accompanied by livedo reticularis (net-like, reddish-blue pattern on the skin). The evolution occurs in a few days to months towards the formation of superficial and deep ulcerations leading to the black eschar, which are intensely painful with centrifuged extension (46). In some patients, pain may precede the skin lesion development. The exact mechanism of pain in calciphylaxis is unclear and is thought to be ischemic in origin, or a neuropathic (nerve damage) component (47).

Lesions develop in areas with abundant adipose tissue (1,48). Ischemic myopathy (muscle damage) is an infrequent manifestation, presenting as painful proximal muscle weakness and can occur without skin necrosis (49).

Laboratory Findings

There are no specific laboratory findings in patients with calciphylaxis.

Biopsy Findings

Skin and fatty tissue arterial calcification, subintimal (inner layer) fibrosis, and thrombotic occlusion of arterioles (7,47,50). Calcification most commonly involves the medial (middle) layer of the arteries, arterioles, and capillaries. However, intimal (inner layer) calcification and calcification of subcutaneous adipose tissue have also been reported (51). Microcalcification detections often require special stains such as von Kossa or Alizarin red (52).

Diagnosis

Calciphylaxis should be suspected in patients with ESKD or advanced chronic kidney disease with painful subcutaneous nodules or plaques, non-healing ulcers, or cutaneous necrosis, particularly in areas with increased adiposity (fatty tissue).
Early stages of calciphylaxis may be misdiagnosed due to the absence of typical clinical features (53).

A skin biopsy may be indicated when a diagnosis of calciphylaxis is uncertain and the patient presents with atypical skin findings (eg. papules, erythema resembling cellulitis), or when patients present early lesions that exhibit characteristic calciphylaxis lesions without having advanced CKD (54). When performing a skin biopsy, samples should be collected from the margin of the lesions, avoiding the direct necrotic area. Skin biopsies are contraindicated if there are suspicions of a superimposed infection.

CT scans have also been performed to detect tissue calcification, but still require further diagnostic evaluation for diagnosis. For further evaluation, a three-phase technetium 99m methylene diphosphonate bone scan can be used as an adjunct to support the diagnosis of calciphylaxis.

Differential Diagnosis

Differential diagnoses include Atherosclerosis, cholesterol embolization, warfarin necrosis, endarteritis obliterans, vasculitis, cellulitis, purpura fulminans, oxalate vasculopathy, antiphospholipid antibody syndrome, cardiac myoma, radiation arteritis, Martorell hypertensive ischemic ulcer, and early-stage nephrogenic systemic fibrosis (47).

Management of Calciphylaxis

There are no US FDA-approved treatments or uniform guidelines for managing calciphylaxis.

Current management strategies include analgesia (pain control), wound care, and mitigation of risk factors. Management is a collaborative task among a dermatologist, a nephrologist, a wound care specialist, and a pain and palliative care specialist. Furthermore, medications such as calcimimetics (parathyroid hormone-reducing agents) are frequently used to treat calciphylaxis, however, their efficacy remains uncertain.

Wound Care and Symptomatic Management

Wound care is one of the most important steps when treating calciphylaxis to limit necrotic (damaged) tissue and prevent infection.

Reported wound-care modalities include enzymatic debridements (dead tissue removal),

non-surgical debridements with maggots, and judicious surgical debridement (55-56). However, the relationship between surgical debridement of calciphylaxis and survival rates is controversial.

Some studies showed better survival among the patients who received surgical debridement but offered no significant impact on early mortality (defined as death within 6 months) (57-58).

Forms of symptomatic management include hyperbaric oxygen therapy, nutritional support, and pain control – which often requires multimodal analgesia and high-dose opioids. Furthermore, additional pain-control agents such as ketamine, benzodiazepines, or spinal anesthetics, and the effective use of cryo-neurolysis of sciatic and prudential nerves have been used to manage intractable pain from calciphylaxis (59-60).

Pharmacotherapeutic Agents

Intravenous Sodium Thiosulfate

Intravenous (IV) sodium thiosulfate (STS) was first reported as a treatment option for calciphylaxis in 2004 (61). Sodium thiosulfate reduces intravascular (inside of blood vessel) and extravascular (outside of blood vessel) calcification burden by chelating (removing by binding) calcium salts and forming a more soluble product, calcium thiosulfate. This process effectively reduces the calcification burden of adipocytes and vascular smooth muscle cells (62-63). IV STS has also been reported to reduce reactive oxygen species (55).

The dosing of IV sodium thiosulfate is variable for patients on hemodialysis (HD). After a test dose of 12.5g is administered, it may be followed by 25g three times a week during the last hour of HD, although other dosing schedules have been reported. A case report presented a successful use of small-dose fractionated STS in a patient undergoing peritoneal dialysis (64).

Intravenous STS has also demonstrated therapeutic success for calciphylaxis in patients with normal kidney function (65). Although there remains a need for more controlled studies to determine the efficacy of sodium thiosulfate, it is frequently used to treat calciphylaxis.

Adverse effects of STS include hypotension, metabolic acidosis, volume overload, hypocalcemia, and QT-interval prolongation (55,66). These adverse effects may be avoided if STS is administered intralesionally (into the lesion) (67). However, there is so far no survival difference between patients with intralesional STS therapy and patients with dual therapy with intralesional and intravenous STS. Furthermore, intralesional injection frequency varies, ranging from a single injection to an injection every few days, with a median quantity of 3.0 ml (68).

SNF472

SNF472 is a hexasodium salt of myo-inositol hexaphosphate. It is an inhibitor of vascular calcification (69). The result of the Phase 3 clinical trial of hexasodium fytate is available. In

patients with calciphylaxis BWAT-CUA and Pain VAS improved. Similarly, in hexasodium fytate and placebo treated patients. Over the course of the entire trial, there were fewer deaths and calciphylaxis related events leading to hospitalization in the hexasodium fytate group.

Biphosphonates

Biphosphonates, which are pyrophosphate analogs, may offer therapeutic benefits for patients with calciphylaxis in the setting of ESKD.

A prospective series of 11 patients with calciphylaxis treated with biphosphonate all showed slowed calciphylaxis progression 2-4 weeks after starting treatment. These patients exhibited significantly improved outcomes compared with those managed with supportive therapies, such as debridement and using low calcium dialysis solution only during HD (70).

Vitamin K

Vitamin K may play a role in the treatment of calciphylaxis as well. The evidence for the positive role of vitamin K in the inhibition of vascular calcification has been explored in clinical trials (Clinical Trail.gov identifier=NCT02278692) (71).

Elimination of Risk Factors

Elimination of risk factors for calciphylaxis is as equally important as active treatment. This includes the withdrawal of warfarin (vitamin K antagonist), vitamin D, and calcium-based phosphate binders (1). Furthermore, optimizing mineral bone disease management by maintaining target ranges of calcium phosphorus, and parathyroid hormone levels for patients with advanced CKD or HD is essential. Replacing activated vitamin D with cinacalcet to keep parathyroid hormone levels in the targeted range, as well as parathyroidectomy for severe refractory hyperparathyroidism are also reasonable approaches (72).

Renal Replacement Therapy

Some case reports state that increased HD treatment frequency resulted in the complete healing of calciphylaxis ulcers (73-74). Kidney transplants, the ideal kidney replacement therapy, also resulted in full resolution of these calcific lesions in isolated case reports (63,75-76).

Experimental Therapies

Several novel and experimental therapies have been evaluated in calciphylaxis and may be used in patients with treatment-resistant lesions (77-79).

A daily low-dose infusion of tissue plasminogen activator was used successfully as adjuvant treatment in a few treatment-resistant patients. Still, many such treatments were complicated by

bleeding (80).

Sterile maggot therapy with larvae of the greenbottle flies, Lucilia sericata has been described as a second-line therapy in case reports (81-82).

Revascularization procedures are not recommended for calciphylaxis treatment.

Vitamin K supplementation was reported as part of a multimodal treatment regimen in 18% of patients from the German Calciphylaxis Registry (18). Data on its efficacy and safety, however, are limited.

Palliative Care

Calciphylaxis is a debilitating condition associated with high morbidity and mortality rates. The use of palliative care provides a multidisciplinary strategy to minimize pain and suffering as goals of care for patients.

Perspectives

Calciphylaxis is a rare disease, however it has high morbidity and mortality. Early diagnosis and termination of offending drugs are crucial as definitive treatments are still under trial. It is well established that the use of acidic olego peptides for bone imaging is an attractive option because they exhibit no apparent side effects and have a shorter half-life invivo compared to biophosphonate (85).

The peptides HA-pep2, HA-pep 3 and HA-pep 7 were identified as having strong and specific affinity to hydroxyapatite (85). They can be used for early diagnosis of calcohylaxis lesion before the appearance of eschar.

Unlike bone targeting and imaging, we can use acidic olego peptide (HA-ep 7), which binds several calcium salt-based materials. That effect is the main intention of calciphylaxis treatment. The peptide-calcium product can be dialyzed out.

Conclusion

Calciphylaxis is a highly lethal disease with high morbidity. The estimated mortality rate is 40% within 6 months and 44% in one year (2,83). Infection is the primary cause of the high mortality associated with this condition, with one report indicating that it accounted for up to 58% of deaths. Ulcerative lesions are particularly severe, carrying a mortality rate of >80% (79). The consequences of unrecognized calciphylaxis can be devastating, underscoring the importance of early diagnosis.

Physicians must consider calciphylaxis as a diagnosis when patients with kidney disease present with a painful skin lesion, even in the setting of acute kidney injury and CKD of allograft (82). A dermatologic evaluation including a histopathological analysis and radiological investigation may help facilitate early diagnosis.

The management of calciphylaxis requires a multimodal and interdisciplinary approach. A trial of pharmacotherapy with sodium thiosulfate should be prioritized. Once a diagnosis is suspected, early withdrawal of risk-inducing medications (warfarin, vitamin D, and calcium-based binders) is essential.

Hyperparathyroidectomy is also an option but can cause severe hypocalcemia, and the effectiveness of cinacalcet in managing uncontrolled hyperparathyroidism is limited. Furthermore, pain control is crucial. While increasing dialysis doses or performing a transplant may be considered, they are not always practical solutions.

More controlled clinical trials are necessary to establish better prevention and treatment of calciphylaxis.

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